Drug Dangers and Reactions

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• **The protection of the consumer against dangerous, adulterated, and misbranded drugs provided by the Federal Food, Drug, and Cosmetic Act has failed in some instances. A general program of reporting adverse drug reactions has been initiated on a pilot basis. Arrangements are being made to extend this program into larger hospitals. Better and more complete reporting of adverse drug reactions together with tightening of the Food and Drug law regarding new drugs will improve this situation.**

Recently the president of the National Academy of Sciences appointed a committee at the request of the Secretary of Health, Education, and Welfare to review the policies and procedures used by the Food and Drug Administration in reaching decisions and to present recommendations. This committee has completed its work and has made specific recommendations that would give the Food and Drug Administration authority to require proof of efficacy as well as safety of all new drugs, and would provide it with sufficient resources to meet the responsibilities assigned to it.

THE FEDERAL FOOD, Drug and Cosmetic Act is intended to protect the consumer against dangerous, adulterated and misbranded drugs and to provide for the safety of new drugs introduced into interstate commerce. In the 22 years since the passage of the Federal Food, Drug and Cosmetic Act of 1938, there have been many situations in which the protection that this act is intended to provide somehow failed.

The original reason for the inclusion of a new drug section in this law was the so-called Elixir of Sulfanilamide® incident. In that case, a manufacturer, attempting to improve his vehicle for the ingestion of sulfanilamide, used an excellent solvent—diethylene glycol—which was tasteless and odorless. Its only drawback was that it was also highly toxic. One hundred eight persons lost their lives because sulfanilamide, diluted with diethylene glycol (which is also the active ingredient in some makes of antifreeze), was introduced as a medicine without proper testing.

After the passage of the 1938 act, it was found that safety might be a goal that is not always attained. One day, the editor of a nationwide medical publication received a manuscript entitled "Coma Due to Sulfathiazole." The authors, two well known eastern physicians, were reporting for the information of the medical profession that several of their patients had gone into coma when given sulfathiazole. This was at a time when sulfathiazole was still a new drug. The editor, sensing some possible discrepancy here, referred the matter to the Food and Drug Administration. Investigation revealed that one of our country's leading drug manufacturers was allowing the "tailings" from batches of phenobarbital (of a famous brand) to slip into the sulfathiazole tablets, just as the corner butcher may let you have some of the hamburger left in the meat grinder from the previous customer. This situation was easily corrected. Another very well known manufacturer of fine chemicals and drugs happened one day to get his cadmium chloride mixed with his calcium chloride because of a labeling mixup, and still another confused cream of tartar with tartaric acid. Fortunately, these errors were detected before the articles reached the consumer.

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One of the most interesting and one of the more sophisticated misbrandings grew out of discovery by one of our largest drug manufacturers that a drug, chemically known as carbaminoyl choline (a cholinesterase inhibitor), would be effective in a dosage of 0.25 mg. as a liquid in a 1 cc. ampul for the relief of postoperative distention. The ophthalmic preparations department of the same firm also found that this same drug, dispensed in 1 cc. ampuls, in powder form, in the amount of 0.15 gm., was an excellent drug for the topical treatment of glaucoma. Both drugs were put out by the same firm in 1 cc. ampuls, one a liquid, the other a powder; both were found to be invoiced as 1 cc. ampuls, and because of the confusion in identifying the proper products on the wards of hospitals, in pharmacies, at wholesalers and all along the line, 15 persons suddenly died unexpectedly. In none of these cases did the attending physician realize what the cause of death was until we made our investigation.

Then it was discovered that the fatal dose of this drug was much less than 150 mg., which was 600 times the intended injectable dose. Death was by pulmonary edema and collapse. A careful control of the production and marketing operation would have prevented these deaths. A criminal prosecution brought a plea of guilty and a maximum fine, but this did not restore life to the deceased.

A few years ago the phenothiazine tranquilizers achieved tremendous publicity as the answer to the problem of mental illness. We know, of course, that the performance was less than the promise, but there was wide use of them—and there still is, as adjuvant therapy, in this disease.

From one hospital, and from one medical school and then from another, we began to receive scattered reports of an "idiosyncrasy to Chlorpromazine," which turned out to be liver damage. Each physician observing such a case thought he was the only one. At one time, it was estimated that liver damage developed in from 1 per cent to 5 per cent of all patients receiving this drug. The Food and Drug Administration was able to require warnings and information concerning the hazards inherent in the use of these drugs, and this information has become common knowledge to the American physician.

The staff available to control and review all the claims, all the evidence as to safety of the drugs produced in this country is pitifully small. A handful of doctors in Washington review new drug applications; an even smaller handful look over the reports concerning existing drugs. There is just being set up a program for general reporting of adverse drug reactions so that there may be at least a central reservoir of information concerning what the drugs—old and new—are doing in the way of unusual reactions.

Five years ago, the Food and Drug Administration began a pilot study on the reporting of adverse drug reactions from ten eastern and midwestern hospitals. From this pilot study, there has grown a program which this year was expanded to bring in reports from various places around the country, where adequate records are kept, of adverse drug reactions as they occur. With the planned expansion of the reporting system, the medical profession and the Food and Drug Administration can learn promptly just what the population of this country is encountering in the way of drug reactions; as soon as these reports are received steps may be taken to protect the physician and the patient from failure of the drug labeling to bear appropriate warnings or instructions.

The Food and Drug Administration is at present attempting to set up such arrangements with several of the larger hospitals in this area. It is also looking at the laws under which it operates and is finding, with the help of interested physicians and others, that these laws may need strengthening, for they were drawn up at times and in situations vastly different from the age of modern science and technology which has changed the whole character of drug production in the past two decades.

Recently, the president of the National Academy of Sciences appointed a committee, at the request of the Secretary of Health, Education, and Welfare, to review the policies and procedures used by the Food and Drug Administration in reaching decisions and to present recommendations. This committee has just completed its work and it has made the following recommendations:

1. The FDA should be given statutory authority to require proof of the efficacy, as well as the safety, of all new drugs. Treatment of a patient with an ineffective drug in place of an effective one may jeopardize his recovery. This is true even though the drug may not be intrinsically harmful, and even though the specific condition for which the drug is given may not be ordinarily regarded as life-threatening.
2. The FDA should be given statutory authority to require manufacturers of new drugs to maintain records and submit reports of clinical experience and other relevant data, not only before but after the drug is released for sale, as requested by the Commissioner in his proposed Factory Inspection and Drug Amendments of 1960. Any evaluation of a new drug is subject to revision in the light of broader experience, and the FDA must be in a position to advise the profession and warn the public promptly whenever new hazards are revealed.
3. The FDA should be given statutory authority to apply certification procedures to all antimicrobial agents used in the prophylaxis and treatment of infectious diseases. The Committee sees no reason for limiting certification to those antibiotic preparations which happen to have come on the market prior to 1950, and further believes that all agents employed for equally serious conditions should be subject to equivalent measures of control.
4. The Committee recognizes the importance to the public health of ensuring that all drugs are prepared under the highest standards of quality control. It, therefore, endorses the Commissioner's proposals in the Factory Inspection and Drug Amendments of 1960 to clarify and strengthen existing inspection authority, and to require that all drugs be manufactured and packaged under adequate controls.
5. The Committee believes that the information supplied to physicians concerning drugs should be not only accurate, but also complete, and that the date of such information is essential to its proper evaluation. It, therefore, endorses the proposed amendments to present labeling requirements published by the Commissioner in the Federal Register for 22 July 1960.
6. The Committee considers that the advertising of pharmaceuticals requires more careful regulation than that of products unrelated to the

prevention and cure of disease. It, therefore, recommends that careful study be given to the problem of coordinating the supervision of labeling, promotional material, and other advertising of drugs, now divided among several agencies of the government, and to means of ensuring that all information concerning drugs conveyed to the profession and the public by whatever media be in conformity with scientific fact.

7. When a decision has been reached concerning an application, a statement should be prepared and incorporated in the file summarizing the conclusions, the names and opinions of those involved, and such other data as may be necessary to provide a concise record of the basis for the decision. This should be of great assistance in the administrative review of current actions and in the scientific review of the files in relation to subsequent applications, as well as when the advice of consultants is sought.
8. The staff members responsible for processing applications should be supported to the utmost in their efforts to obtain submission of truly dependable scientific information on the efficacy and safety of the products. The data initially submitted by the manufacturer are not always of sufficient quality and quantity to permit a sound decision as to the merits of the product.
9. The FDA should be strongly supported in its effort to maintain a research program of high quality on the methodology and standardization of drug testing and related areas of basic science. This is important not only to improve the methods available for carrying out its responsibilities to the public but also as an aid in recruiting and retaining competent scientists on the staff.
10. The Committee urges the Commissioner to seek such authorization as may be necessary to establish an advisory organization of scientific and technical experts as a recognized resource for advice on criteria, procedures and policies for the execution of the responsibilities of the FDA.
11. It is recognized that these various recommendations cannot be carried out without expanded resources, both of funds and of personnel. The committee also considers that the present resources of the FDA are less than adequate to meet existing responsibilities. It, therefore, urges that the FDA be granted the authority and funds required to employ and retain larger numbers of highly qualified personnel and to support their activities, and endorses the recommendations made to this end by the Citizens' Advisory Committee in 1955.

The Secretary of the Department of Health, Education and Welfare has concurred with all these recommendations, except No. 6, which he has requested be given further study. When these recommendations are implemented, there will be, I hope, fewer drug reactions and dangers, and those that do occur will be recognized much sooner.

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